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Worcester Polytechnic Institute

Artemisia annua L. GRAS Research

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FDA GRAS *Artemisia*

March 9, 2017

Professor Pamela J. Weathers, Advisor

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Abstract

Plants are a common source of new medicinal compounds. This paper is focused on documenting the safety of one such species, *Artemisia annua* L., as an antimalarial treatment. Malaria is a dangerous disease especially common in tropical areas, which are quite often developing countries. Medicinal use of *A. annua* is known to have occurred as early as 168 B.C. In China where it was used to treat multiple ailments. In more modern history, an extract of the plant called artemisinin was recognized as an effective antimalarial medicine. However, recent research showed that a treatment involving consumption of the whole plant material not only has greater efficacy but also reduces the risk of the parasites developing resistance. It is intended that the dried leaves be used as an orally or rectally administered tablet made up of ground and compressed dried leaf material. In order to aid in determining the safety of using the dried leaves of *A. annua* as a treatment for malaria, information regarding the plant's safety was acquired and collated in the form of an FDA GRAS proposal. GRAS is an acronym used by the U.S. Food and Drug Administration that represents "Generally Regarded As Safe" and means that a substance is safe enough to be excluded from food additive requirements. By structuring this report in the form of a GRAS proposal, it can reasonably be expected that the breadth and validity of the reported information will be sufficient to demonstrate the safety of *A. annua*. Information regarding safety of *A. annua* was obtained from a number of sources including books, scientific papers, government documents, and internet web sites. Assessment of reports of the plant's chemical composition showed that no compound naturally present in *A. annua* would produce ill side effects given the anticipated level of consumption. *A. annua*, like many plants, can absorb heavy metals from the soil, and their over accumulation can be harmful. That being said, *A. annua* is currently sold by multiple companies as a dietary supplement in the United States and is also eaten as part of salads in some Asian countries. It is also considered to be a safe plant according to Dr. James A. Duke, an American botanist and author of numerous publications. In conclusion, *Artemisia annua* L. is safe enough to satisfy the GRAS rating and be used in the future as an antimalarial treatment made up of the whole plant material.

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1.0 Description

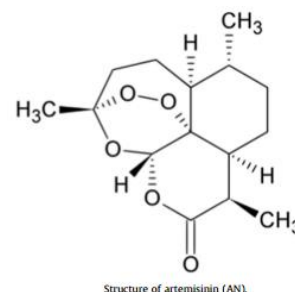
Artemisia annua L. is an annual plant that has a native range from Eastern Europe all the way to Vietnam, but has now naturalized over much of the world (Royal Botanical Gardens). It has a single woody stem that grows about one meter in height. The plant has smaller branches with green leaves that are divided into three leaflets. The flowers grow in small buds with an outer green layer and the inside petals are usually yellow (Royal Botanical Gardens). The leaves, floral buds and flowers also have glandular trichomes where the drug artemisinin is produced and stored (Lommen et al. 2006).

1.1 History

The earliest known use of *A. annua* is as early as 168 B.C. in China where it is called *Qing Hao* (Hongwen and Shouming, 2002). It was used for treating “hemorrhoids, lice, wounds, boils, sores, ‘lingering heat in joints and bones’ as well as ‘exhaustion due to heat/fevers’” (Hsu, 2006a). The last two ailments are common symptoms of malaria, so the plant was likely used to treat malaria long before modern times (Hongwen and Shouming, 2002). According to the ancient Chinese Materia Medica, the plant was prepared by soaking it in water and then wringing it out, this would expel the juice from the plant into the water, which was then simply ingested in its entirety (Hsu, 2006b).

1.2 Modern Research

A. annua is also a vital medicinal herb in modern medicine primarily for extraction of artemisinin, one of its main phytochemicals. Artemisinin is a sesquiterpene lactone with a peroxy group that is produced in the glandular trichomes of the plant (Ferreira and Janick 1995). The peroxy



Structure of artemisinin (AN).

(Desrosiers and Weathers, 2016)

group has been determined to be an essential for therapeutic activity (Li, 2012). Artemisinin was isolated from *A. annua* by Chinese scientists and has proven successful at treating malaria. The drug is now delivered as part of a combination therapy (ACT, artemisinin combination therapy) where an artemisinin derivative is combined with another antimalarial drug, e.g. artemether + lumafantrine in Coartem® (Nosten and White, 2007; Wilairatana et al. 2002). For discovery of artemisinin, the lead of the project, Tu Youyou, was one of the recipients of the 2015 Nobel Prize in Medicine. The Chinese effort started as Project 523, a secret military program to find a cure for malaria, which was a major cause of death in China's southern provinces (Miller and Su, 2011). The project was split into two groups, one to develop synthetic compounds, and the other to examine traditional Chinese medicine. The second group, led by Tu Youyou, screened more than one hundred different herbs until inspired by a text called *Emergency Prescriptions Kept up one's Sleeve* by Ge Hong, written in 340 A.D (Hsu, 2006a). The text called for preparing the plant using only low heat as opposed to more common herbal teas or infusions, which used boiling water. The research team tested its effectiveness on mice and monkeys with success, until moving onto a human clinical trial in August 1972 where twenty-one patients were cured of malaria (Hsu, 2006b). Due to the military origins of the project, the researchers were unable to share their findings with non-Chinese scientists until after Project 523's eventual end in 1981. The Walter Reed Army Institute of Research was the first to produce artemisinin outside of China and lead the way for its commercial use (Weina, 2008).

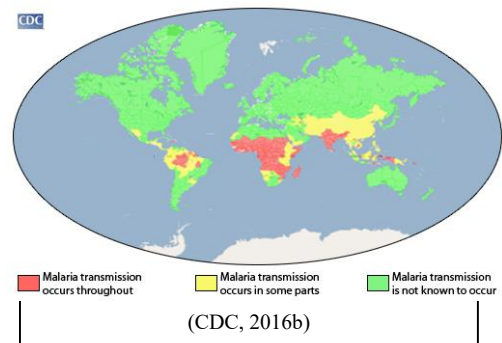
1.3 Production

Artemisinin can be produced both naturally and semi-synthetically although the natural method is far more common. Synthetic production of artemisinin is done through the use of genetically engineered yeast, which are cultured in large bioreactors and produce artemisinic

acid, a precursor to artemisinin (Peplow 2016). Natural production involves growing, harvesting, and processing *A. annua* from which artemisinin is extracted. The best time to harvest the plant is at the start of flowering when artemisinin content in the leaves is highest (WHO, 2005). There are other factors such as geographical conditions, harvesting time, and fertilizer application that can also affect production (WHO, 2005). The highest artemisinin content that can be expected is 1-2% of dry weight of leaf (WHO, 2005). After the crop is harvested, it is cleaned of foreign matter, sprayed with water, and cut into sections. The plants are then dried either in the sun, shade, or through the use of an oven. The branches are finally shaken or struck to release the leaves so that they may be collected (WHO, 2005). There are several viable methods for extraction of artemisinin from *A. annua* and is most commonly done with solvents such as supercritical carbon dioxide or hexane, which are relatively cost effective methods (Lapkin et al. 2006).

1.4 Malaria

Malaria is one of the world's most problematic diseases in tropical areas, especially in developing countries. In 2015 for example, there was an estimated 214 million cases worldwide with approximately 438,000 deaths (CDC, 2016a). It is caused by several species of parasitic protozoa: *Plasmodium falciparum*, *P. vivax*, *P. ovale*, and *P. malariae* (Wilairatana



et al. 2002). The parasites are spread by mosquitos that infect humans through a bite. The *Plasmodium*, in the form of sporozoites, travels through the infected person's blood stream to the liver where they asexually reproduce (Warhurst, 2007). The resulting offspring are merozoites, which travel back into the bloodstream, infect red blood cells, and continue to asexually

reproduce (Warhurst, 2007). The blood cell hosts are destroyed by this process. Some of the merozoites instead develop into gametocytes, which are then taken up into a new mosquito when the human host is bitten again (Warhurst, 2007). The gametocytes differentiate into male and female genders and sexually reproduce in the mosquito, completing the lifecycle.

Common symptoms of malaria include fever, chills, sweats, headaches, muscles pain, nausea, and vomiting (CDC, 2016a). More severe malaria can cause confusion, coma, neurologic focal signs, severe anemia, and respiratory difficulties (CDC, 2016a). Pregnant women are of particular concern as malarial infection is linked with stillbirths, infant mortality, abortion, and low birth rate (Hartman, 2010). The particular benefit of artemisinin has been its effectiveness in treating the disease when the parasites have developed resistance to the previous antimalarial medications including chloroquine, mefloquine, halofantrine and a combination of quinine and tetracycline; artemisnins also do not cause significant side effects like pyrimethamine and sulfonamide (Wilairatana et al. 2002). Patients using the latter drugs such as chloroquine and may experience stomach pain or nausea and mefloquine can cause seizures, visual disturbances and psychosis (CDC, a; CDC, b). Unfortunately, regular use of artemisinin also is resulting in emergence of artemisinin drug resistance.

1.5 Whole Plant Treatments

Recent research however, has started to show that consumption of the dried leaves of *A. annua* is actually more effective in the treatment of malaria due to increased bioavailability of artemisinin found within the plant and in response to other antimalarial phytochemicals such as 1,8-cineole, limonene, and flavonoids, that work with artemisinin to be effective against resistant parasites (Elfawal et al. 2012; Weathers et al. 2014). Whole plant treatments have been shown to be effective against artemisinin resistant parasites potentially because of these additional

phytochemicals (Elfawal, 2015). The various active ingredients within the whole leaf material means that the treatment is not a mono therapy and resistance will develop slowly, if at all (Elfawal et al. 2015). One of the most promising effects of this whole plant treatment is that it kills the sexually active gametocytes that survive in the patient even after other treatments have cured them from the disease (Wright et al. 2002). These gametocytes can be transmitted into mosquitos that have bitten the host, which are then eventually transmitted back into other humans; this is how the disease is able to spread despite treatment (Bousema et al. 2006). *A. annua* can even be used to make an essential oil that has shown significant antimicrobial effect (Juteau et al. 2002).

Much of the population that suffers the most from malaria lives in developing countries, where antimalarial medications are often difficult to obtain and expensive to purchase if available. The higher cost of manufacturing artemisinin medications can place the drug out of reach for some patients so a switch to use of much more affordable whole plant treatments could provide many more people with access to this life saving medication.

1.6 GRAS Rating

“Any substance that is intentionally added to food is a food additive, that is subject to pre-market review and approval by FDA, unless the substance is generally recognized, among qualified experts, as having been adequately shown to be safe under the conditions of its intended use” (FDA GRAS, 2004).

This official recognition of safety by the FDA is called a GRAS rating (Generally Recognized As Safe). The rating would allow for the rated substance to be added to food, or otherwise ingested, with fewer restrictions and less difficulty getting review from the FDA. A GRAS rating is attained by submitting a report to the FDA what a particular substance should

have the rating. The submission includes identity, intended use, manufacture process, historical use in food before 1958 and clinical studies showing its safety.

1.7 Objective

The goals of this project are to collect information regarding the safety of *Artemisia annua* L. for ingestion and compile it in a format as if for a GRAS submission. Although the document will not actually be submitted to the FDA, the material will now be assembled in one public location.

1.8 Methodology

For a substance to receive a GRAS rating the FDA requires proof that ingestion of the substance causes no adverse effects and/or that it has been in long term general use. Common acceptance of a substance as GRAS by experts in the field is also relevant information the FDA would consider. In the case of substances used in food before January 1, 1958, experience based on common use can also act as evidence. This means proof of long spread cultural use as food would also be applicable.

There is already a general consensus among experts that *A. annua* L. is safe for consumption in reasonable amounts. It has been used to create herbal teas and infusions in traditional and modern Chinese medicine (Räth, 2004). Whole plant matter has been used in studies to test for efficacy in treatment of malaria, and it is even listed as GRAS, for use as a food additive, in the *Handbook of phytochemical constituents of GRAS herbs and other economic plants* by J. Duke (2001). Still, as much evidence as possible needs to be gathered to include in the notice from sources such as books, scientific journals, and data from the internet. Besides

using library resources, communicating with people from the FDA itself will also be another avenue of information.

The final step of the project will be to collate our combined research into a format fitting that of a final GRAS notice. We have determined that *A. annua* is already qualified for a GRAS rating because the entire *Artemisia* genus is listed as long as the food product is thujone-free (Appendix A). Thujone is a monoterpene neurotoxin that can cause death after consumption (Cobb, 1922). *A. annua* is a species that does not contain or produce thujone so it is allowed by this restriction.

GRAS Notice

2.0 GRAS sections

Necessary elements of an FDA GRAS Notice

- Introductory information about the submission.*
- Information about the notifier.*
- General administrative information.*
- Intended use.
- Identity.
- Method of manufacture.
- Specifications.
- Dietary exposure.
- Self-limiting levels of use.
- Common use in food before 1958.
- Comprehensive discussion of the basis for the GRAS determination.
- Bibliography.
- Signature

*These sections have been determined to not be needed at this time because this notice draft is at present only an academic exercise.

2.1 Intended use

The dried plant leaves and small bits of stem of *A. annua* L. are intended to be used as a medicinal herb for the treatment of malaria. The plant has many possible methods of use including as compressed dried leaf tablets, encapsulated dried leaf powder and precisely prepared tea infusion all of which are taken orally. The pure drug can also be delivered rectally via capsules, although this leads to less effective absorption (Titulaer et al. 1990). Encapsulation has not shown a significant decrease in the absorption of artemisinin or flavonoids but some foods such as peanut butter did decrease absorption (Desrosiers and Weathers, 2016). The plant is intended for consumption by the general population of adults, and children that are infected with malaria. Children too young to swallow tablets can ingest the drug via nasogastric tube or rectally.

2.2 Identity

The dried leaf material of *A. annua* L. is commonly known as “sweet annie, sweet wormwood, sweet sagewort, annual mugwort, annual wormwood, or in Chinese, pinyin: qinghao” (Weathers, 2015). *A. annua* is native to Southeast Asia and China, growing naturally in the steppes of Chahar and Suiyuan at about 1000 m above sea level (Ferreira and Janick, 2009). The plant has however now been naturalized over much of the world (Royal Botanical Gardens). It has a single woody stem that grows about one meter high. It has smaller branches that grow green leaves that are divided into three leaflets. The flowers grow in small buds with an outer green layer and the inside petals are usually yellow (Royal Botanical Gardens).

2.3 Production

A. annua is grown around the world including Argentina, France, Italy, and China and has been naturalized in the United States, it is best suited to open sunny areas with limited rainfall (Royal Botanical Gardens). For extraction of artemisinin, plants are usually grown on plantations or small plots, harvested and dried, and then shipped to various sites where the leaves are processed to extract the artemisinin (Hongwen and Shouming, 2002). The best time to harvest the plant is at the start of flowering when the floral buds have formed and the artemisinin content in the leaves is highest (WHO, 2005). There are other factors such as geographical conditions, harvesting time, and fertilizer application that can also affect production (WHO, 2005). The highest artemisinin content that can be expected is 1-2% of dry weight of leaves (WHO, 2005). After the crop is harvested, it is cleaned of foreign matter, sprayed with water and cut into sections. The plants are then dried either in the sun, shade or through the careful use of an oven. The branches are finally shaken or struck to release the leaves so that they can be collected (WHO, 2005). The dried leaf material is then crushed into fine powder, mixed so that the material is homogenous and pressed into tablets (ICIPE, 2005). The material can also be made into capsules, which show no signs of decreasing artemisinin bioavailability, but do mask the bitter taste of the leaf material (Desrosiers and Weathers, 2016). Powdered leaf tablets are the preferred form for oral ingestion because artemisinin is then more bioavailable, there is greater antimalarial efficacy from orally ingested plant material, and there is more resiliency against emergence of artemisinin drug resistance (Weathers et al. 2011; Elfawal et al. 2012, 2015).

2.4 Chemical Composition

The chemical composition of *A. annua* will vary based on the cultivar, soil chemistry, climate and season. However, Iqbal et al. (2012) provides an example of the general composition of the plant (Table 1).

Table 1: Chemical composition of *Artemisia annua* leaves (Iqbal et al. 2012)

Contents	Amount (% dry weight basis)
Ash	7.5
Carbohydrate	8.3
Fat	6.07
Fiber	14.2
Moisture	11.4
Protein	24.37 mg/100g
Phytate	140.4 mg/100g
Total Tannins	0.61 mg/100g
Tocopherol	2.74 mg/100g

The essential oil of *A. annua* comprises 0.4% to 4.0% of the composition of the leaves by weight (Bilia et al. 2014). The type and concentration of the compounds that make up the oil varies widely over geographic regions and can also be affected by the drying temperature (Tzenkova et al. 2010). Listed in Table 2 are many of the compounds known to be present in the essential oil with an estimated percentage of composition by weight, and, where known, the oral LD50 of those components.

Table 2: Chemical Composition of *Artemisia annua* essential oil (Tzenkova et al. 2010; Azimova and Glushenkova, 2012)

Compound	Estimated % of Total EO	Oral LD50	Reference
Aldehydes	12	N/A	
L- β -Artemisia alcohol	4	N/A	
Tiglate artemisia alcohol	N/A	N/A	
Artemisia ketone	8.45	N/A	
Artemisia triene	0.25	N/A	
Borneol	<0.	Mouse 3720 mg/kg	(Science Lab 2013b)
α -Bourbonene	<0.1	N/A	
Cadinene	1.03	Rat >5000 mg/kg	(Vigon. 2015a)
Camphene	0.4	Rat >5 g/kg	(Tisseran. 1995)
Camphor	3.61	Mouse 1310 mg/kg	(Toxnet 2015a)
Cappilene	N/A	N/A	
Carene	0.2	Rat 4800 mg/kg	(Vigon. 2015d)
Carvacrol	80	Rat 810 mg/kg	(Spectrum. 2006b)
Caryophyllene	24.73	N/A	
Caryophyllene oxide	N/A	N/A	
α -Cedrene	0.28	N/A	
Cineole	10.0-25.0	Mouse 3849 mg/kg	(Xu. 2014)
1,8-Cineol (Eucalyptol)	2.55	Rat 2480 mg/kg	(Science Lab. 2013a)
Corymbolone	<0.1	N/A	
Cuminaldehyde	16	Rat 1320 mg/kg	(TCI. 2014)
α -Cuebene	13.53	N/A	
p-Cymene	1.73	Rat 4750 mg/kg	(Toxnet. 2013)
α -Elemene	3.41	N/A	
Eugenol	<0.1	Rat 1930 mg/kg	(Science Lab. 2013c)
Farnesene	2.23	Rat 5628 mg/kg	(Spex. 2016)
α -Humulene	3.68	Rat >48 mg/kg	(Drug Future)
Isoaromadendrene epoxide	<0.1	N/A	
cis-Lanceo	0.26	N/A	
Ledene oxide	1.39	N/A	
Limonene	0.7	Rat 5 g/kg	(Filipsson. 1998)
Linalool	2.2	Rat 2790 mg/kg	(Karlaganis. 2002)
Menthol	N/A	Rat 2900 mg/kg	(Science Lab. 2005)
Menthylacetate	N/A	Rat > 5000 mg/kg	(Vigon. 2015c)
3-Methylpinocarvone	N/A	N/A	
Muurolene	0.54	N/A	
Myrsene	N/A	Rat >5000 mg/kg	(Spectrum. 2006a)
Myrsenol	N/A	Rat 3600 mg/kg	(Vigon. 2015b)
Ocimene	N/A	Rat >5 g/kg	(Tisseran. 1995)

Trans-ocimene	<0.1	N/A	
Phellandrine	<0.1	Rat 5700 mg/kg	(EMD. 2013)
α -Pinene	1.26	Rat 3700 mg/kg	(Santa Cruz. 2008)
β -Pinene	23.7	Human 0.5-5 g/kg	(Toxnet. 2009)
Pinocampheol	N/A	N/A	
Trans-pinocarveol	0.43	N/A	
Pinocarvione	N/A	N/A	
Pinocarvone	0.73	N/A	
Pinocarvylacetate	N/A	N/A	
Psuedopinene	0.32	Rat 4700 mg/kg	(Lewis. 1990)
α -Selinene	8.21	N/A	
β -Selinene	25	N/A	
Sylvestrene	<0.1	N/A	
Terpineol-4	N/A	Rat > 2000mg/kg	(ECA)
α -Terpineol	<0.1	Rat 5170 mg/kg	(Toxnet 2015b)
Terpinen-4-ol	<0.1	Rodent 1.0-4.3 g/kg	(Acros. 2009b)
α -Terpinene	N/A	Rat 1680 mg/kg	(Acros. 2015)
γ -Terpinene	<0.1	Rat 3650	(Sigma. 2016)
Thymol	80	Rat 980 mg/kg	(Santa Cruz. 2010)
Ulangene	N/A	N/A	

Note. N/A means not available.

Heavy metals are another potentially toxic material that may be detected in *A. annua*. These elements are taken up through the roots from contaminated soil or water and thus the concentrations vary across different agricultural regions. For example, arsenic can produce harmful effects in humans with as little as 5 mg consumed orally, causing vomiting and diarrhea (Kingston. 1993). The oral human LD50 of arsenic is estimated to be 70-180 mg (Table 3; EPA. 1978). Cadmium has an oral LD50 in rats of 2,330 mg/kg (ACI Alloys). Zinc toxicity occurs from ingestion of >255mg (Toxnet). The oral LD50 of zinc for humans is estimated at 3g/kg (Acros, 2009a). Nickel likewise requires a large ingested amount to be dangerous with an oral LD50 for rats of >9,000 mg/kg (Acros, 2010). Lead has an oral LD50 in humans of 450 mg/kg (CDC, 1994). Long term lead exposure is also a concern. The FDA recommends a maximum lead level of 0.1 ppm in candy for example (FDA, 2006). The LD50 of pure mercury is not

known but for mercuric chloride, the oral LD50 for rats is 25.9-77.7 mg/kg (DHHS, 1999). Table 3 shows an example of heavy metal concentrations of plants sampled from Gopeshwar, India along with US EPA acceptable limits.

Table 3: Concentration of Heavy Metals by Dry Plant Weight (Negi et al. 2012)

Sample	Plant Part	As mg/kg	Cd mg/kg	Zn mg/kg	Ni mg/kg	Pb mg/kg	Hg mg/kg
<i>A. annua</i>	Leaves	1.82	0.30	18.00	1.22	1.24	1.60
	Roots	1.86	0.36	27.00	3.02	1.84	1.92
Acceptable Limits for Water (mg/L)							
EPA limits		0.01	0.005	5.000	0.100	0.005	0.002

Acceptable Limits Source: (FDA, 2016)

2.5 Dietary Exposure

As of February 23, 2017, liquid extracts (<https://www.swansonvitamins.com/swanson-premium-full-spectrum-wormwood-425-mg-90-caps>) and aerial shoot parts of *A. annua* in capsules (<http://www.iherb.com/pr/herb-pharm-artemisia-annua-1-fl-oz-29-6-ml/12681>) are available for purchase in the U.S. from Swanson Vitamins. The Full-Spectrum Wormwood aerial parts supplement is advertised as 425 mg capsules of dried *A. annua* and has been on the market since 2007. *A. annua* capsules are also sold by Solaray as a dietary supplement (<http://www.vitacost.com/solaray-sweet-wormwood-100-vegetarian-capsules-2>). Capsules of 98.5% pure artemisinin can purchased from Better Health International and are listed as containing no thujone (http://www.betterhealthinternational.com/productDetails.asp?prodID=NC55400&utm_medium=shoppingengine&utm_source=shopzilla).

2.6 Self-limiting levels of use

The dried leaf material is expected to be consumed in 500 mg tablets of dried leaf powder with up to 10 tablets per day for five days. The patients that participated in a study that used this regimen reported no adverse effects (ICIPE, 2005). The LD50 for *A. annua* taken as gel capsules in mice is 162.5g/kg (Wan et al. 1992), however, that study used crude extracts of the plant and not just the dried leaf powder.

2.7 Dietary uses pre 1958

Sweet Wormwood, despite being bitter tasting to many, is reportedly eaten as part of salads in some Asian countries (Tompa, 2008). About 25% of individuals do not perceive the plant as tasting bitter and actually find the taste pleasant (Desrosiers and Weathers, 2016).

2.8 Historical use in medicine

The earliest known use of *A. annua* is as early as 168 B.C. in China where it is called *Qing Hao* in the Chinese *Materia Medica* (Hongwen and Shouming, 2002). It was used for treating “hemorrhoids, lice, wounds, boils, sores, ‘lingering heat in joints and bones’ as well as ‘exhaustion due to heat/fevers’” (Hsu, 2006a). The last two ailments are common symptoms of malaria so the plant might have been used to treat malaria long before modern times (Hongwen and Shouming, 2002). According to the ancient Chinese *Materia Medica*, the plant was prepared by soaking it in water and then wringing it out. This process would expel the juice from the plant into the water which was then simply ingested in its entirety (Hsu, 2006b).

2.9 Acceptance by Experts

A. annua is botanically accepted as being a safe plant. It is listed in the *Handbook of phytochemical constituents of GRAS herbs and other economic plants* by James A. Duke and even has listed dosages of 30g of dry leaf per day (Duke, 2001). This dosage is 10-30 times greater than the maximum anticipated dosage per day for treating malaria.

2.10 GRAS Status for *Artemisia* genus

The *Artemisia* genus of plants already has a GRAS status with the FDA, as long as the final product is thujone-free (Appendix A). Thujone is a monoterpene found in a number of *Artemisia* species e.g. *A. absinthium*, which is used in the production of absinthe. At high enough dosages, thujone is a neurotoxin that can lead to convulsions, unconsciousness, and death in humans (Cobb, 1922). However, *A. annua* is a species that contains no thujone and therefore the thujone restriction does not limit *A. annua* use (Tzenkova et al. 2010).

2.11 Conclusions

To our knowledge there is no inherent risk to consuming dried *A. annua* either as a supplement or as part of a malarial treatment with the exception of the possible presence of heavy metals at concentrations higher than recommended by the FDA. Such an issue can be resolved however, by growing the plants with soil and water that do not contain enough of these substances to bioaccumulate to harmful levels by the time the leaves are harvested. Regular testing of the harvested material would also be prudent. This report can be used not only as a source to demonstrate the safety of *Artemisia annua* L. consumption but also potentially as part of a future effort to have the FDA specifically recognize *A. annua* as a GRAS substance.

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Appendix A

<p style="text-align: center;">TITLE 21--FOOD AND DRUGS CHAPTER I--FOOD AND DRUG ADMINISTRATION DEPARTMENT OF HEALTH AND HUMAN SERVICES SUBCHAPTER B--FOOD FOR HUMAN CONSUMPTION (CONTINUED)</p> <p>PART 172 -- FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION</p> <p>Subpart F--Flavoring Agents and Related Substances</p> <p>Sec. 172.510 Natural flavoring substances and natural substances used in conjunction with flavors.</p> <p>Natural flavoring substances and natural adjuvants may be safely used in food in accordance with the following conditions.</p> <p>(a) They are used in the minimum quantity required to produce their intended physical or technical effect and in accordance with all the principles of good manufacturing practice.</p> <p>(b) In the appropriate forms (plant parts, fluid and solid extracts, concentrates, absolutes, oils, gums, balsams, resins, oleoresins, waxes, and distillates) they consist of one or more of the following, used alone or in combination with flavoring substances and adjuvants generally recognized as safe in food, previously sanctioned for such use, or regulated in any section of this part.</p>		
Common name	Scientific name	Limitations
Alce	Alce pernyi Baker, A. barbadensis Mill., A. ferox Mill., and hybrids of this sp. with A. africana Mill. and A. spicata Baker	
Althea root and flowers	Althea officinalis L	
Amyris (West Indian sandalwood)	Amyris balsamifera L	
Angola weed	Roccella fuciformis Ach	In alcoholic beverages only
Arnica flowers	Arnica montana L., A. fulgens Pursh, A. sororia Greene, or A. cordifolia Hooker	Do.
Artemisia (wormwood)	Artemisia spp	Finished food thujone free ¹

(FDA, 2016)